UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

ISIS PHARMACEUTICALS, INC., a Delaware Corporation, Plaintiff, v. SANTARIS PHARMA A/S CORP., a Delaware Corporation, and SANTARIS PHARMA A/S, a Danish Corporation, Defendants. AND RELATED COUNTERCLAIMS.	Case No. 3:11-cv-2214-GPC-KSC **ORDER DENYING DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT** **(ECF NO. 195)**

INTRODUCTION

Plaintiff Isis Pharmaceuticals, Inc. (Isis) alleges defendants Santaris Pharma A/S Corp. and Santaris Pharma A/S (together, Santaris) have infringed three of Isis's patents by offering to sell certain drug discovery and development services to several U.S. pharmaceutical companies. (ECF No. 130, First Am. Compl. (FAC).) Before the Court is Santaris's renewed Motion for Summary Judgment of Noninfringement (Motion) pursuant to 35 U.S.C. § 271(e)(1)'s so-called "safe harbor." (ECF No. 195.) Isis has opposed Santaris's Motion, (ECF No. 223), and Santaris has filed a reply, (ECF No. 244). The Court found Santaris's Motion suitable for disposition without oral

argument. See CivLR 7.1.d.1. Having considered the parties' submissions, the record in this matter, and the applicable law, and for the reasons that follow, the Court will **DENY** Santaris's Motion.

BACKGROUND

To avoid duplicative efforts, this Court sets forth the background information of this case as described in Judge Moskowitz's September 19, 2012 Order Denying Defendants' Motion for Summary Judgment Without Prejudice. (See ECF No. 53 at 1-5.) The Court modifies the background provided by Judge Moskowitz as necessary to reflect the additional facts Isis has since alleged in its FAC. (See ECF No. 130.)

The three patents at issue in this litigation cover various forms of antisense technology. The Court thus provides an overview of antisense technology, the three patents-in-suit, and Plaintiff's specific infringement claims.

I. Overview of Antisense Technology

Proteins, fundamental molecules found in all living cells, are primary actors within a cell. They perform a variety of essential functions such as catalyzing chemical reactions, communicating between cells, and providing structural support. The overproduction or abnormal production of proteins can cause disease. One method for treating a disease caused by the overproduction of a certain "target" protein is to create an "antisense" molecule that interrupts the cellular process of creating that protein.

The cellular process of creating proteins begins with genetic information (genes) stored in DNA and proceeds in two stages: transcription and translation. During transcription, the gene for a particular protein is copied from a strand of DNA to a molecule called messenger RNA (mRNA). During translation, cellular machinery converts the information on the mRNA into proteins.

Antisense molecules—typically a type of a nucleic acid that is similar to DNA and mRNA molecules, but much shorter—are able to interrupt the genesis of the target protein at the translation stage by binding to the mRNA molecules containing the genetic information for that protein. Once bound to an mRNA molecule, the antisense

molecule can obstruct the chemical process that translates the mRNA into a protein. The three biotechnology patents at issue in this litigation relate to antisense technology.

II. Patents

A. '199 Patent

U.S. Patent No. 6,326,199, "Gapped 2' Modified Oligonucleotides" or "gapmers" ('199 Patent), claims, in independent claim 1, a method of enhancing an antisense molecule by creating structural features that (a) enable the antisense molecule to resist degradation before it reaches its target mRNA; (b) enhance "binding affinity" (i.e., the strength of the chemical bond between the antisense molecule and the target mRNA); and (c) activate an enzyme called Rnase H that, once activated, severs the target mRNA, preventing translation into the target protein. (See FAC ¶¶ 20-22; '199 Patent Col. 31, ll. 39-49.) Many of the dependent claims cover methods of modifying the molecule described in Claim 1.

Independent claim 11 claims a method of "modifying a sequence-specific ribo-nucleic acid" (i.e., a target mRNA or other type of RNA) using a molecule having the properties claimed in claim 1. ('199 Patent Col. 33, ll. 3-15.) In other words, claim 11 covers the method of using the antisense molecule described in claim 1 to affect the function of its target.

B. '500 Patent

U.S. Patent No. 6,066,500, "Antisense Modulation of Beta Catenin Expression" ('500 Patent), is directed toward antisense technology that is designed specifically to inhibit the expression of a protein called Beta catenin. Beta catenin has been implicated in the development of several types of cancer, including cancer of the colon and of the skin. Independent claims 1 and 3 cover an antisense molecule of a particular size that hybridizes with the mRNA molecule responsible for generating Beta catenin, and thereby "inhibits the expression of Beta catenin." (Col. 65, ll. 53-54.) Many of the dependent claims cover a more specific type of molecule that meets the qualifications of the molecule described in claims 1 and 3.

Claims 11 and 20 cover a "method of inhibiting the expression of human Beta catenin in human cells or tissues comprising contacting said cells or tissues in vitro with the antisense compound of [claims 1 and 3] so that expression of Beta catenin is inhibited." (Col. 66, ll. 56-59; Col. 68, ll. 3-6.)

C. '739 Patent

U.S. Patent No. 6,440,739, "Antisense Modulation of Glioma-Associated Oncogene-2 Expression" ('739 Patent), is directed toward antisense technology that is designed specifically to inhibit the expression of a protein called glioma-associated oncogene-2. This protein is associated with a number of human development syndromes and cancer. (FAC ¶ 24.) Independent claims 1 and 3 cover an antisense molecule of a certain size that hybridizes with the mRNA molecule responsible for generating glioma-associated oncogene-2, thereby inhibiting the expression of that protein. (Col. 83, ll. 25-41.)

Claims 14 and 23 cover methods of inhibiting glioma-associated oncogene-2 by contacting cells in vitro with the antisense molecules covered in claims 1 and 3. (Col. 84, ll. 25-29, 49-54.)

III. Isis's infringement claims

Isis alleges that Santaris, in direct competition with Isis, "engages in the business of selling antisense drug discovery services and products to pharmaceutical company customers in the United States." (FAC ¶ 25.) Isis alleges that, as part of these "drug discovery services," Santaris used the methods covered by the '199 Patent "as a research tool to identify targets and/or to screen . . . antisense molecules for activity inhibiting a target." (Id. ¶ 26.) Isis alleges that "Santaris's business has been built around exploiting the platform technology pioneered and patented by Isis, and selling and offering it for sale to pharmaceutical companies." (Id.)

Isis further alleges that "Santaris has offered for sale and sold to Enzon Pharmaceuticals, Inc., antisense compounds that inhibit beta-catenin and glioma-associated oncogene-2 production in violation of the '500 Patent and the '739 Patent,

respectively." (Id. ¶ 28.)

Isis alleges four specific agreements between Santaris and pharmaceutical companies based in the United States form the basis of these infringement contentions:

January 4, 2011 announced agreement with Pfizer, Inc. Isis alleges Pfizer paid Santaris "$14 million for access to Santaris Pharma A/S Locked Nucleic Acid (LNA) Drug Platform to develop RNA-targeted drugs." (Id. ¶ 41 (quoting FAC Ex. 4, Jan. 4, 2011 Press Release).) Pfizer also allegedly "agreed to pay milestones [up to $600 million] to Santaris upon the identification of up to ten gene targets and the discovery of lead antisense LNA molecule candidates."[1] (FAC ¶ 41.)

This agreement allegedly infringes the '199 patented methods by "[o]ffering for sale and selling the process of using gapmers to reduce target RNA for target validation purposes; and/or [o]ffering for sale and selling the process of screening and identifying gapmer compounds to identify drug candidates for drug development." (Id. ¶ 43.)

July 27, 2006 announced agreement with Enzon Pharmaceuticals, Inc. Plaintiff alleges Santaris "sold two antisense gapmer molecules and targets to Enzon for $6 million," (id. ¶ 46), and that, pursuant to the agreement, "Enzon nominated six additional targets for which Santaris agreed to identify LNA gapmer compounds that inhibit the nominated targets using Isis's methods patented in the '199 Patent and compositions covered in the '500 and '739 Patents." (Id. ¶ 47.)

This agreement allegedly infringes the '199 patented methods and the '500 and '739 patented compositions and methods by "[o]ffering for sale and selling the process of using gapmers to reduce target RNA for further drug discovery; [o]ffering for sale or selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development; and/or "[s]elling, offering to sell, and/or importing antisense compounds specific for beta-catenin and/or glioma-associated oncogene-2

[1] Isis alleges "this agreement represented an expansion of a 2009 agreement with Wyeth in which $7 million was paid to Santaris up front plus a potential $83 million in additional milestone payments." (Id. ¶ 41.) Isis alleges "Pfizer acquired Wyeth in 2009," and thus refers to both entities as "Pfizer." (Id.)

in or into the United States." (Id. ¶ 50.)

August 24, 2009 announced agreement with Shire PLC. Pursuant to this agreement, Santaris allegedly "would 'receive significant upfront payments, milestone payments and royalties for providing access to [Santaris's] LNA technology' and exclusivity for three targets and an additional two targets to be nominated by Shire in the future." (Id. ¶ 52 (quoting FAC Ex. 7, Aug. 24, 2009 Press Release).)

Isis alleges this agreement infringes the '199 patented methods by "[o]ffering for sale and selling the process of using gapmers to identify and reduce target RNA for further drug discovery; and/or [o]ffering for sale and selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development." (Id. ¶ 53.)

December 19, 2007 announced agreement with GlaxoSmithKline. Isis alleges that, pursuant to this agreement, "Santaris would receive approximately $8 million as an upfront payment, milestone payments, and royalties for providing access to Santaris's LNA technology and exclusivity for four targets." (Id. ¶ 50.)

Isis alleges this agreement infringes the '199 patented methods by "[o]ffering for sale and selling the process of using gapmers to identify and reduce target RNA for further drug discovery; and/or [o]ffering for sale and selling the process of screening and identifying gapmer candidates to identify drug candidates for drug development." (Id. ¶ 58.)

Based on the foregoing allegations, Isis asserts three causes of action for direct and/or induced infringement of the '199, '500, and '739 Patents. (Id. ¶¶ 60-78.)

At the inception of this case, Santaris moved for summary judgment on its affirmative defense that the acts of infringement alleged in Isis's initial Complaint fell within the safe-harbor set forth in 35 U.S.C. § 271(e)(1) and that Santaris was therefore exempt from infringement liability. (ECF No. 17.)

In denying Santaris's Motion for Summary Judgment, Judge Moskowitz found Santaris's evidence on the safe-harbor issue "f[ell] short of the evidentiary burden

placed on an accused infringer claiming exemption from infringement under § 271(e)(1)." (ECF No. 53 at 8.) Santaris had largely relied on the declaration of one of its officers, Dr. Henrik Ørum, which provided a general description of the collaborations between Santaris and its pharmaceutical collaborators in the United States, but which did not provide a "specific analysis of Santaris's uses of the allegedly infringing compounds, methods, and processes." (Id.)

Judge Moskowitz further found that Isis had "called into question Santaris's claim that 'Santaris does not perform any antisense technology work until a therapeutic target has been identified by someone else.'" (Id.) In that vein, Judge Moskowitz noted that Dr. Ørum's had stated to the USPTO that, "The majority of [Santaris's] collaborators have taken broad licenses to our proprietary LNA platform in order to discover, develop, and commercialize new LNA-based drugs against RNA targets associated with disease." (Id. at 9.) Judge Moskowitz concluded that, "[t]o the extent [that] Santaris is selling and/or licensing infringing 'platform' technology so that another company can 'discover and develop' drug candidates—rather than developing and/or licensing/selling specific drug candidates itself—Santaris could be using or selling patented technology to perform 'basic scientific research' [which is not exempt under § 271(e)(1)]." (Id.)

Based on the foregoing, Judge Moskowitz denied Santaris's Motion for Summary Judgment without prejudice and granted Santaris leave to renew its motion for summary judgment after a period of discovery limited to Santaris's safe-harbor defense. That limited period of discovery has concluded, and Santaris has filed a renewed motion for summary judgment on its safe-harbor defense ("Motion"). (ECF No. 195.)

LEGAL STANDARD

Summary judgment is appropriate where the moving party demonstrates the absence of a genuine issue of material fact and entitlement to judgment as a matter of law. Fed. R. Civ. P. 56(c); Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986). A fact

is material when, under the governing substantive law, it could affect the outcome of the case. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986); Freeman v. Arpaio, 125 F.3d 732, 735 (9th Cir. 1997). A dispute about a material fact is genuine if "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." Anderson, 477 U.S. at 248.

A party seeking summary judgment always bears the initial burden of establishing the absence of a genuine issue of material fact. See Celotex, 477 U.S. at 323. "Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment." T.W. Elec. Serv., Inc. v. Pac. Elec. Contractors Ass'n, 809 F.2d 626, 630 (9th Cir. 1987).

DISCUSSION

Santaris asserts that its Motion presents a single question: "If, as Isis contends, offering and executing the collaboration and license agreements in the United States could constitute acts of infringement, is Santaris nevertheless protected by the statutory 'Safe Harbor' for drug development?"[2] (ECF No. 213, Santaris Mot. at 1-2.) Santaris asserts the answer is yes for two reasons: (1) the terms of Santaris's various agreements with its U.S. collaborators "call[] for one or both parties to design and develop drugs, generate data, and use such data to apply for FDA approval of promising drugs"; and (2) "Santaris believed at the time of the 'offer and sale' of the Collaborations that it would conduct certain types of in vitro experiments in Denmark to generate the type of data relevant to FDA submissions." (Id. at 3.)

In opposition, Isis argues disputes of material fact abound with regard to whether Santaris's collaboration agreements were—at the time of execution—"reasonably related" to the type of information submitted to the FDA. Isis further contends disputes of material fact also exist with regard to whether Isis's patented technology is a "patented invention" within the scope of § 271(e)(1). (ECF No. 239, Isis Opp'n at 2.)

[2] Santaris notes that, if its Motion is denied, it plans to file a motion to dismiss on the issue of whether the offer and execution of collaboration and license agreements constitute acts of infringement.

I. 35 U.S.C. § 271(e)(1)'s Safe Harbor[3]

Generally, one infringes a patent when one "makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor." 35 U.S.C. § 271(a). It is not, however, "an act of infringement to . . . use . . . or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the . . . use . . . of drugs." Id. § 271(e)(1). The Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) is one such "Federal law which regulates the . . . use . . . of drugs." Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193, 196 (2005) (hereinafter, Merck I).

Section 271(e)(1) was one of two statutes enacted by Congress "to eliminate two unintended distortions of the effective patent term resulting from premarket approval required for certain products by the FDA." Proveris Scientific Corp. v. Innovasystems, Inc., 536 F.3d 1256, 1260 (Fed. Cir. 2008); Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990). One of the distortions was a reduction in the period during which a patented invention could be marketed to generate profits. Proveris, 536 F.3d at 1260. This resulted from the fact that patents are usually obtained early in the regulatory process, while marketing approval generally comes years later.[4] Id. at 1260-61. The second distortion was a de facto extension of the effective patent term. Id. at 1261. This resulted from the fact that competitors were prohibited from undertaking activities involving a patented invention until after the patent expired, which meant that patent holders could market their inventions without competition while competitors were only

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[3] Isis suggests Judge Moskowitz's recitation and application of the legal concepts and rules relevant to § 271(e)(1) is the law of the case. Application of the "law of the case" doctrine, however, does not necessarily apply in this situation, as "[a]ll rulings of a trial court are 'subject to revision at any time before the entry of judgment.'" United States v. Houser, 804 F.2d 565, 567 (9th Cir. 1986) (citing Fed. R. Civ. P. 54(b)). This Court thus expands on the legal framework and analysis that Judge Moskowitz provided as set forth herein.

[4] The statute enacted to remedy this first distortion is found at 35 U.S.C. § 156. It provides for an extension of a patent term for a product that "has been subject to a regulatory review period before its commercial marketing or use."

just able to begin the years-long regulatory approval process. Id.

Thus, "[t]he basic idea behind [§ 271(e)(1)] was to allow competitors to begin the regulatory approval process while the patent was still in force, followed by market entry immediately upon patent expiration." Id. at 1262; see also Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520, 1525 (Fed. Cir. 1992) ("By permitting the testing and regulatory approval process to begin well before a controlling patent had run its course, Congress must have intended to allow competitors to be in a position to market their products as soon as it was legally permissible."). Indeed, "[e]very decision examining the statute has appreciated that § 271(e)(1) is directed to premarketing approval of generic counterparts before patent expiration." Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1071 (Fed. Cir. 2011).

Merck I is the primary Supreme Court case on the safe harbor's application to the use of patented biological compounds. Because the parties rely extensively on Merck I, the Court provides a full exposition of the case here, after which the Court will address additional contours of the safe harbor.

The Supreme Court in Merck I decided whether § 271(e)(1)'s safe harbor protected a drug developer, Merck KGaA (Merck); a researcher, Dr. David Cheresh(Dr. Cheresh); and a research institute, Scripps Research Institute (Scripps), from infringement liability for their use of certain peptides in their efforts to develop an angiogenesis inhibiting drug. "Angiogenesis is the process by which new blood vessels sprout from existing vessels; it plays a critical role in many diseases, including solid tumor cancers." Merck I, 545 U.S. at 197.

In his initial research, "Dr. Cheresh succeeded in reversing tumor growth in chicken embryos," first using an antibody he developed and later using peptides provided by Merck. Id. All of the peptides Merck provided to Dr. Cheresh were later determined to be covered by five patents held by Integra Lifesciences, Ltd. (Integra). Id. at 197 n.3.

Based on this initial research, Dr. Cheresh orchestrated an expanded

collaboration between Merck and Scripps. Id. at 198. The collaboration agreement set forth a 3-year timetable in which to develop angiogenesis inhibitors, "beginning with in vitro and in vivo testing of [the covered peptides] at Scripps in year one and culminating with the submission of an IND to the FDA in year three." Id. Merck pledged $6 million over three years to fund the research. Id. The agreement "specified that Scripps would be responsible for testing [the covered peptides] produced by [Merck] as potential drug candidates but that, once a primary candidate for clinical testing was in 'the pipeline,' [Merck] would perform the toxicology tests necessary for FDA approval to proceed to clinical trials." Id.

Pursuant to the expanded collaboration agreement, "Dr. Cheresh directed in vitro and in vivo experiments on [the covered peptides] provided by [Merck]." Id. These experiments focused on three closely related peptides within the larger set of the covered peptides "and were designed to evaluate the suitability of each of the peptides as potential drug candidates." Id. "[T]he tests measured the efficacy, specificity, and toxicity of the particular peptides as angiogenesis inhibitors, and evaluated their mechanism of action and pharmacokinetics in animals." Id. at 199.

Based on the foregoing research, Merck selected a lead candidate and "initiated a formal project to guide [the lead candidate] through the regulatory approval process." Id. Merck shared its peptide research with the National Cancer Institute (NCI). Id. While the NCI ultimately filed an IND and agreed to sponsor clinical trials, Merck decided not to proceed with the regulatory approval process. Id.

Before Merck shared its research results with the NCI, however, Integra filed a patent-infringement suit in the Southern District of California against Merck, Dr. Cheresh, and Scripps. Id. at 200. Merck answered that its use of the covered peptides fell within § 271(e)(1)'s safe harbor. Id.

After a trial, the district court concluded that all but one of the activities conducted before the parties entered into the expanded collaboration agreement fell within the safe harbor. Id. The district court found an issue of fact remained as to

whether Merck's use of the covered peptides after the parties entered into the expanded collaboration agreement fell within the safe harbor. The court thus gave the following jury instruction:

> To prevail on this defense, [the defendant] must prove by a preponderance of the evidence that it would be objectively reasonable for a party in [the defendant's] . . . situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.
>
> Each of the accused activities must be evaluated separately to determine whether the exemption applies.
>
> [The defendant] does not need to show that the information gathered from a particular activity was actually submitted.

Id. at 200-01.

The jury found that Merck, Dr. Cheresh, and Scripps failed to show their activities were protected by § 271(e)(1) and awarded Integra $15 million in damages. Id. at 201. In deciding post-trial motions, the district court found the evidence sufficient to show that "any connection between the infringing Scripps experiments and FDA review was insufficiently direct to qualify for the [safe harbor exemption]." Id.

On appeal, the Court of Appeals for the Federal Circuit affirmed in part and reversed in part, agreeing the safe harbor did not apply because "the Scripps work sponsored by [Merck] was not clinical testing to supply information to the FDA, but only general biomedical research to identify new pharmaceutical compounds." Id.

Ultimately, the Supreme Court granted certiorari to review the Federal Circuit's construction of § 271(e)(1). The Supreme Court began its analysis of § 271(e)(1) by recognizing that, while "the contours of this provision are not exact in every respect, the statutory text makes clear that it provides a wide berth for the use of patented drugs in activities related to the federal regulatory process." Id. at 202 (emphasis added). Indeed, the exemption "extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA." Id. "This necessarily includes preclinical studies of patented compounds that are

appropriate for submission to the FDA in the regulatory process," as "[t]here is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included." Id.

With regard to preclinical research (i.e., research done before testing on humans), the Supreme Court declined to limit the type of information relevant to FDA submissions to "that which pertains to the safety of the drug in humans." Id. at 203. Rather, the Supreme Court recognized the FDA requires IND applicants to include summaries of the drug's pharmacological, toxicological, pharmacokinetic, and biological qualities. Id. (citing 21 CFR § 312.23(a)(5); U.S. Dept. of Health & Human Servs., Guidance for Indus., Good Clinical Practice: Consolidated Guidance 45 (Apr. 1996)). The Supreme Court further recognized that, given the FDA's goal of determining whether a drug poses an "unreasonable risk," "the FDA does not evaluate the safety of proposed clinical experiments in a vacuum." Id. at 203-04 (citing 21 U.S.C. § 355(i)(3)(B)i); 21 CFR §§ 312.23(a)(8) & 56.111(a)(2)). This requires an IND applicant to "provide sufficient information for the [FDA] investigator to 'make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed [clincial] trial.'" Id. at 204 (citing Guidance for Indus., supra). "Such information necessarily includes preclinical studies of a drug's efficacy in achieving particular results." Id.

With this as a foundation, the Supreme Court did not take exception to the Federal Circuit's conclusion that the exemption "does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Id. at 205. In this vein, the Supreme Court explained:

> Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce, is surely not "reasonably related to the development and submission of information" to the FDA.

Id. at 205-06 (quoting § 271(e)(1)). The Supreme Court was careful to note, however,

that "[i]t does not follow from this . . . that § 271(e)(1)'s exemption . . . categorically excludes (1) experimentation on drugs that are not ultimately the subject of an FDA submission or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA." Id. at 206. "Under certain conditions, [the Court] think[s] the exemption is sufficiently broad to protect the use of patented compounds in both situations." Id.

The Supreme Court noted that

> [t]he relationship of the use of a patented compound in a particular experiment to the 'development and submission of information' to the FDA does not become more attenuated (or less reasonable) simply because the data from that experiment are left out of the submission that is ultimately passed along to the FDA. Moreover, many of the uncertainties that exist with respect to the selection of a specific drug exist with respect to the decision of what research to include in an IND or NDA.

Id. at 207.

While the Supreme Court took no issue with the Federal Circuit's "basic scientific research" limitation, the Supreme Court did take issue with the Federal Circuit's emphasis on the fact that the "Scripps-Merck experiments did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA process." Id. at 205. The Supreme Court found the Federal Circuit's reliance on this fact "disregard[ed] the reality that, even at late stages of the development of a new drug, scientific testing is a process of trial and error." Id. at 206. The Supreme Court thus concluded:

> Properly construed, § 271(e)(1) leaves adequate space for experimentation and failure on the road to regulatory approval: At least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particularly biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is "reasonably related" to the "development and submission of information under . . . Federal law."

Id. at 207 (quoting § 271(e)(1)) (emphasis added).

With the foregoing in mind, the Supreme Court agreed "that the use of patented compounds in preclinical studies is protected under § 271(e)(1) as long as there is a

reasonable basis for believing that the experiments will produce 'the types of information that are relevant to an IND or NDA.'" Id. at 208 (emphasis added). The Supreme Court thus vacated the Federal Circuit's judgment and remanded the matter for an evaluation of the evidence under a proper construction of § 271(e)(1). Id.

On remand, the Federal Circuit found each of Merck's allegedly infringing activities fell within the safe harbor. Integra Lifesciences, Ltd. v. Merck KGaA, 496 F.3d 1334, 1347 (Fed. Cir. 2007) (hereinafter, Merck II). In doing so, the Federal Circuit rejected Integra's attempt to classify Merck's activities as "discovery" or "routine," with "only those experiments devoid of discovery, and entirely routine, . . . be[ing] subject to the FDA Exemption." Id. The Federal Circuit explained, "the safe harbor does not depend on a distinction between 'discovery' and 'routine,' but on whether the threshold biological property and physiological effect had already been recognized as to the candidate drug." Id. (citing Merk I, 545 U.S. at 202). The Federal Circuit recognized, "The variety of experimental activity that may apply to any specific biologic or physiologic investigation reinforces the fact-dependency of the inquiry." Merck II, 496 F.3d at 1347 (emphasis added).

Having discussed Merck I and Merck II, the Court next addresses two specific contours of the safe harbor. The first pertains to the phase of regulatory approval in which the patented invention is used. In Classen Immunotherapies, Inc. v. Biogen IDEC, a case decided after Merck I and Merck II, the Federal Circuit found § 271(e)(1) inapplicable to certain patented studies undertaken after FDA approval of certain vaccines to evaluate the association between the timing of childhood vaccinations and the risk of certain disorders. 659 F.3d 1057, 1070 (Fed. Cir. 2012). While information from the studies could have been submitted in response to the FDA's requirement that "adverse experience information" be reported with regard to the vaccines, the studies were not mandated by the FDA and did not facilitate marketing a drug by "expedit[ing] development of information for regulatory approval." Id. The Federal Circuit thus held that the use of a patented invention to obtain information that may, but is not

required to, be reported to the FDA after marketing approval has been obtained does not fall within the safe harbor.

In Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc., another case decided after Merck I and Merck II, the Federal Circuit held that a generic drug manufacturer's use of a patented invention in quality control tests conducted and submitted to the FDA in order to satisfy the FDA's requirement that each batch of the generic drug sold after the FDA's initial approval be the bio-equivalent of the reference (i.e., brand name) drug fell within § 271(e)(1)'s safe harbor. 686 F.3d 1348 (Fed. Cir. 2012). In reaching its decision, the Momenta court recognized the Supreme Court's guidance in Merck I that the safe harbor's applicability is not limited by the phase of research (e.g., pre-/post-FDA marketing approval) in which the patented invention is used or the particular FDA submission in which information derived from the invention's use could be included. Id. at 1356. The Momenta court therefore concluded that, even though the generic drug manufacturer's use of the patented quality control tests occurred after the FDA's initial approval of the generic drug, the use of the test fell within the safe harbor because it resulted in information that the FDA required the manufacturer to collect and retain for inspection.

The Court reads Classen and Momenta as standing for the proposition that, regardless of the stage of the regulatory process in which a patented invention is used to obtain information, the information derived from using the patented invention must be "reasonably related" to the type of information required by the FDA at some point during the regulatory process. This is indeed a "wide berth." Merck I, 545 U.S. at 202.

Another contour of the safe harbor pertains to the term "patented invention" as used in § 271(e)(1). See Proveris, 536 F.3d 1256, 1265 (Fed. Cir. 2008). The term was first addressed by the Supreme Court in Eli Lilly & Co. v. Medtronic, where the Court was tasked with deciding whether the term "patented invention" included medical devices. 496 U.S. at 663-63. Ultimately, the Supreme Court interpreted the term "patented invention" to at least include "all inventions" within the ambit of 35 U.S.C.

§ 156, (see n.3, above). 496 U.S. 661, 673-74 (1990). The inventions within the ambit of § 156 are those eligible for patent term extension, including medical devices. The Supreme Court thus concluded that the use of medical devices may fall within the safe harbor.

Later, in AbTox, Inc. v. Exitron Corp., the Federal Circuit held that the term "patented invention" includes any medical device, regardless of its eligibility for patent term extension under § 156. 122 F.3d 1019, 1028-29 (Fed. Cir. 1997).

Then, in Proveris, the Federal Circuit decided whether the use of a device that measured spray patterns fell within the safe harbor, given that the device was, on one hand, not subject to FDA approval itself but, on the other hand, was used to obtain information relevant to FDA regulatory submissions.[5] 536 F.3d at 1265. Because the device was sold only to pharmaceutical companies and the FDA, it was undisputed that the use of the device by the pharmaceutical companies and the FDA was "reasonably related" to FDA submissions. It was disputed, however, that the device manufacturer's marketing and sale of the device to pharmaceutical companies and the FDA was "reasonably related" to FDA submissions because the manufacturer was not itself engaged in the FDA process.

In determining whether the device fell within the safe harbor, the Federal Circuit recognized that § 271(e)(1) and 35 U.S.C. § 156, (see n.3, above), "operate in tandem" to remedy the two distortions of patent terms discussed above. 536 F.3d at 1263 n.4 (citing Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 672-73 (1990)). On that basis, the Federal Circuit found that, because the device was neither eligible for a patent extension under § 156 nor subject to the FDA process, it followed that the use of the invention needed no exemption from infringement liability under § 271(e)(1). 536 F.3d at 1265-66. The Federal Circuit thus concluded that the device was not a "patented invention" under § 271(e)(1).

[5] The device measured the parameters of aerosol sprays used in nasal spray drug delivery devices, which devices are subject to FDA approval.

In PSN Illinois, LLC v. Abbott Laboratories, the district court relied on Proveris to find the safe harbor inapplicable where an accused infringer used patented protein receptors as a "research tool," which the court defined as "tools that scientists use in the laboratory including cell lines, monoclonal antibodies, reagents, animal models, gro[w]th factors, combinatorial chemistry and DNA libraries, cloning tools . . . , methods, laboratory equipment, and machines." 2011 WL 4442825, at *4 n.1 (N.D. Ill. Sept. 20, 2011) (quotation marks omitted) (citing Merck II, 496 F.3d at 1347 n.3). Relying on Proveris, the court explained that the defendants "were not infringing on the [protein] receptors in order to obtain FDA approval to introduce a generic receptor to compete in the marketplace when the patent on those receptors expired." 2011 WL 4442825, at *6. Rather, the defendants "were using a patented invention to develop their own patentable product." Id. The court thus concluded that, "because the [protein] receptors do not require regulatory approval, they are not a 'patented invention' within the meaning of § 271(e)(1)."[6, 7]

Here, the Court concludes that disputes of material fact exist with regard to whether Santaris's collaboration agreements are "reasonably related to the development and submission of information" to the FDA and whether the methods and compounds claimed in the '199, '500, and '739 Patents are in fact "patented inventions" under § 271(e)(1).

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[6] Santaris argues Momenta, 686 F.3d 1348 (Fed. Cir. 2012), abrogates Proveris with regard to whether a patented invention that is not itself subject to regulatory approval is considered a "patented invention" for purposes of § 271(e)(1). That issue, however, was not before the Momenta court. Thus, the court in Momenta did not have the opportunity, as the court in Proveris did, to review the legislative history and purpose underlying § 271(e)(1) with regard to what constitutes a "patented invention."

[7] Santaris also relies on Teva Pharmaceuticals USA, Inc. v. Sandoz Inc., 2013 WL 3732867 (S.D.N.Y. July 16, 2013), to argue that (1) Proveris applies only where the accused infringer is "not itself engaged in development and submission of information under a federal law," and (2) PSN Illinois is either "wrong or irrelevant." Having considered Teva, this Court disagrees with its limited reading of Proveris and its complete rejection of PSN Illinois. Despite the Proveris court's lengthy discussion of what constitutes a "patented invention" under § 271(e)(1), the Teva court would find the Proveris court's holding sui generis. 2013 WL 3732867, at *8 ("Proveris is a case which cannot be separated from its factual context."). This Court does not read Proveris so narrowly and, on that basis, finds PSN Illinois to be persuasive authority.

Santaris asks the Court to conclude, as a matter of law, that the collaboration agreements it entered into with its U.S. collaborators are themselves "reasonably related" to FDA submissions. It is largely undisputed, however, that—at the time Santaris entered into these agreements—its U.S. collaborators had identified few, if any, of the targets Santaris would be attempting to modify using antisense technology. (See Santaris Mot. at 10.) Moreover, because Santaris was to develop a library of antisense compounds for each selected target, the specific compounds Santaris would be using to modify each of the selected targets were also unknown. (See id.) Santaris's activities are therefore distinguishable from the infringing activities in Merck I.

In Merck I, Dr. Cheresh had succeeded in reversing tumor growth in chicken embryos using an antibody he developed before using any peptides covered under Integra's patents. It was based on this initial research that Merck entered into the expanded collaboration agreement with Scripps, under which Dr. Cheresh's experiments focused on three closely related peptides.

While Santaris may have had a reasonable basis for believing generally that one or more antisense molecules could affect one or more targets selected by its U.S. collaborators, Santaris has presented no evidence that, at the time it entered into the collaboration agreements, it knew of the "particular biological process" and "particular physiological effect" that using Isis's patented inventions would have in relation to how each antisense compound in its libraries would affect each target. To the contrary, the collaboration agreements generally required Santaris to (1) wait for its U.S. collaborators to select a target, (2) develop a library of antisense compounds for each selected target, and (3) screen each compound in the library for its effects on a given target using, among other tools, Isis's patented inventions. Then, after even more work by the U.S. pharmaceutical companies, information from Santaris's research results might be submitted to the FDA in connection with an IND.

These facts make it appear Santaris is taking a position on § 271(e)(1) that the Federal Circuit warned against—a position that views the safe harbor as "globally

embrac[ing] all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Merck I, 545 U.S. at 205.

While an accused infringer may not always be required to have a "reasonable basis for believing" a patented invention will have a "particular biological effect" through a "particular biological process" before coming within the safe harbor,[8] Santaris has not presented undisputed evidence demonstrating that its collaboration agreements themselves rest on such a reasonable basis. Given the dissimilarities between the facts of this case and those of Merck I, the Court is not prepared to conclude, as a matter of law, that Santaris's collaboration agreements fall within the safe harbor. Therefore, what is left to determine is whether Santaris's collaboration agreements are "reasonably related" to the type of information submitted to the FDA—that is, whether it was "objectively reasonable for a party in [Santaris's] . . . situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question." See Merck I, 545 U.S. at 200-01 (district court jury instruction). The Court finds this question is, as with most questions involving a determination of what is reasonable, best left to the trier of fact. See Merck II, 496 F.3d at 1347 (noting "fact-dependency" of safe-harbor inquiry).

The Court further finds that disputes of material fact exist with regard to whether the methods and compounds covered by the patents-in-suit are "patented inventions" for purposes of § 271(e)(1). The Court finds Santaris has not offered undisputed evidence that Isis's patented methods and compounds are themselves subject to regulatory approval. See Proveris, 536 F.3d at 1265-66. In other words, considering the purpose of § 271(e)(1), the Court finds Santaris has not offered undisputed

[8] The Supreme Court in Merck I, stated that otherwise infringing acts come within the safe harbor "[a]t least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular biological effect . . . ." 545 U.S. at 207. The use of "at least" means, as Santaris asserts, that these facts are sufficient, though not necessarily required, to come within the safe harbor.

evidence that its use of Isis's patented inventions "is directed to premarketing approval of generic counterparts before patent expiration." Classen, 659 F.3d at 1071. Instead, the evidence Santaris has offered demonstrates Santaris's use of Isis's patented technology is directed toward creating its own patented inventions. See PSN Illinois, 2011 WL 4442825, at *6.

CONCLUSION & ORDER

Based on the foregoing, the Court concludes Santaris has not demonstrated that it is entitled to a judgment of noninfringement as a matter of law under § 271(e)(1). Accordingly, **IT IS HEREBY ORDERED** that:

1. Santaris's Motion, (ECF No. 195), is **DENIED**;
2. This case shall proceed in due course.

DATED: February 27, 2014

HON. GONZALO P. CURIEL
United States District Judge